IOSR Journal of Applied Physics (IOSR-JAP)
e-ISSN: 2278-4861.Volume 8, Issue 2 Ver. I (Mar. - Apr. 2016), PP 44-52
www.iosrjournals.org

Evaluation of The Second Cancer's Risk In Conformal Therapy And Intensity Modulated Radiotherapy For The Organs Inside The Primary Radiation Fields

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Abstract: *Evaluation of the second cancer's risk in conformal therapy and intensity modulated radiotherapy for the infield and out of field organs from the primary radiation fields. Material and methods: planning studies on two group of patients, first group suffering from prostate cancer and other group suffering from breast cancer, each patient has two plans one 3DCRT and the other IMRT plan, The analysis of data based on isodose distributions, Dose Volume Histograms (DVHs) by taking mean absorbed doses for each organ in 3DCRT and IMRT and using them to calculate: 1) Lifetime Risk, 2) Excess Relative Risk (ERR) and, 3) Excess Absolute Risk (EAR). Results showed increase in dose for out of field OAR with IMRT plan comparing to 3D-CRT where in IMRT larger volume is irradiated to lower doses because the total MUs in IMRT is higher than that of 3D-CRT which increase probability of induce of second primary cancer in out of field OAR in IMRT than in 3D-CRT while for infield OARs with IMRT receives lower dose allowing significant reduction in the doses in infield OAR compared to 3D-conformal radiotherapy.*

Keywords: *prostate cancer and breast cancer, radiation induced second primary cancer*

I. Introduction And Background

The radiation therapy technique has developed significantly over the last few decades. We have moved from simple 2 dimensional treatment to 3 dimensional conventional radiotherapy using the treatment fields to an increasingly conformal radiotherapy technique based on three dimensional computed tomography (CT) information such as three dimensional conformal therapy (3DCRT) and intensity modulated radiotherapy (IMRT). [(1)]

Primary and secondary radiation Radiation to normal tissues consists of primary radiation,the direct result of the treatment beams, as well assecondary radiation, which largely affects out-of-fieldtissues.In photon treatments, secondary radiation results fromscatter from within the patient and from the collimator,as well as leakage from the treatment machine [(2, 5)]. Close to the target, scatter from within the patient is the main source of secondary radiation, while further from the target, leakage photons are important [(2)]. At higher photon energies (≥10MV), neutrons are produced from high density materials within the machine head and these may make a significant contribution to out-of field secondary dose [(6)].

Prostate cancer (PCa) is the most common cancer in men in Europe and accounts for over one fifth of male cancer diagnoses. Radiotherapy is one treatment option for localised and locally advanced PCa and may be delivered as external beam radiotherapy (EBRT), brachytherapy (BT) or combination EBRT and BT (EBRT-BT). Survival following radical radiotherapy has improved over the last decade, as a result of dose escalation and use of androgen deprivation. As survival improves, long term consequences of treatment become more relevant. One of the most serious long term effects following radiotherapy is development of a radiation induced second primary cancer (RISPC). Newer radiotherapy techniques such as IMRT have facilitated dose escalation, but differences in dose distribution and scatter have raised theoretical concerns about an increased risk of RISPC [(7)].

The increasing use of intensity modulated radiotherapy (IMRT), and the associated increasein whole body exposure to low doses from scattered and leakage radiation, has generatedinterest on the possible risks of second cancer induction for patients receiving curativeradiotherapy.This issue has become of consequence because of the success of moderntechniques, including radiotherapy, in increasing life expectancy for many patients withcommon cancers. The implications for prostate patients have been examined by a number ofgroups, whilst other have assessed the risks to pediatric patients, and patients under 40 years. Early breast cancer patients have an expectation of good long term survival and contribute alarge radiotherapy treatment group. There has been an increasing use of modern methodsfor the treatment of early breast cancer. Many authors have

published IMRT techniques for whole breast treatments and three clinical trials using IMRT have reported dosimetric, medium and long term follow up.Baglan et al 21 described a method using non coplanar conformal planning for accelerated partial breast irradiation (ABPI) and several groups have reported methods for simultaneous integrated boost (SIB) treatments. The increased complexity of these techniques compared to standard whole breast radiotherapy (WBRT), potentially increases the dose to non-target tissue. In addition, there is often a need to use Image Guided Radiotherapy (IGRT), for example, in partial breast irradiation (PBI), or to achieve specific planning target volume (PTV) margins[(8)].

The move from 3D-CRT to intensity modulated radiation therapy (IMRT) involves more fields, and the dose–volume histograms show that, as a consequence, a larger volume of normal tissue is exposed to lower doses. In addition, the number of monitor units is increased by a factor of 2 to 3, increasing the total body exposure, due to leakage radiation. Both factors will tend to increase the risk of second cancers. Altogether, IMRT is likely to almost double the incidence of second malignancies compared with conventional radiotherapy from about 1% to 1.75% for patients surviving 10 years. The numbers may be larger for longer survival, but the ratio should remain the same. According to HALL J et al (2003), radiation-induced carcinomas, there is likely to be an increased incidence for IMRT compared with 3D-CRT due to the dose distribution, i.e., a larger volume irradiated to lower doses. It is estimated that an additional 0.5% of surviving patients will develop a second malignancy as a result of this factor. There will also be an increased incidence for IMRT due to an increase in monitor units. It is estimated that an additional 0.25% of surviving patients will develop a radiation-induced malignancy because of this factor. [(9)]

II. Material And Methods

In this study 25 patients of different age were planned with both 3D-CRT and IMRT. The patients were of two different sites of tumors (Breast cancer and Prostate cancer).Measurements & calculation performed with these treatments to evaluate the expected doses to OARs.

Clinical planninginformation:Patients were planned on XiO 4.64 (Computerized Medical Systems, St. Louis, MO, USA) using the superposition algorithm.

Conformal planning: Treatment plans were created for 6, 10 MV or 6, 15 MV photons. All fields were shaped at the beam's eye view to encompass the PTV shape using multileaf collimator (MLC).The treatment target volume included the PTV and an additional 0.7-cm margin for beam penumbra in all directions.

Inverse-planned IMRT:plans were generated using commercial inverse planning software. The beams are spread around the target with equal space and to avoid the opposing fields an odd numbers of the treatment fields were used.

Evaluation of treatment planning dosefrom dose volume histograms (DVHs) for maximum, minimum and mean dosesto appreciate dose received to the different structures in different treatment plans.For OARs evaluate mean dose in Gray(Gy) and convert it to Sievert(Sv) then use it to calculate Excess relative risk (ERR) and Excess absolute risk (EAR) for cancer incidence.

According to the Radiation Therapy Oncology Group (RTOG): Organs At Risk (OARs):

Prostate cancer under RTOG protocol 0126; The Rectal criteria require that no more than 15%, 25%, 35%, and 50% of the rectum volume should receive More than 75 Gy, 70 Gy, 65 Gy, and 60 Gy respectively. For the bladder, the guidelines require no more than 15%, 25%, 35%, and 50% of the bladder volume should receive more than 80 Gy, 75 Gy, 70 Gy, and 65 Gy respectively.

Breast cases: The dose for the planning target volume (PTV) was 50 Gy; ipsilateral lung had a dose–volume constraint of 20 Gy, 20%; no more than 20% of ipsilateral lung receiving 20 Gy or more.

Estimation of the risk of secondary cancer based on incidence data for OARs under study requires firstly calculating the equivalent doses for these organs using the following equation. $H_T = \sum W_R D_{T,R}$,Where H_T is the equivalent dose of organ T in Sv, $D_{T,R}$ is the mean absorbed dose from radiation R in a tissue or organ T, W_R is the radiation weighting factor and it is equal to 1 for photons. Since W_R is dimensionless, the unit for the equivalent dose is the same as for absorbed dose, J kg-1, and its special name is Sievert (Sv). [(10)]

III. Risk Models For Radiation- Induced Cancer

Excess Relative Risk (ERR) and /or Excess Absolute Risk (EAR) models were developed for cancer incidence. The radiation risk models developed by ICRP Publication 103 for use in its 2007 recommendations based on incidence data from the life span study (LSS) of Japanese bomb survivors. [(10)]

Excess relative risk (ERR) and /or excess absolute risk (EAR) models were developed for cancer incidence and mortality incidence as a function of age at exposure and sex, for ten specific organs: breast, lung, stomach, colon, red bone marrow (RBM), bladder, liver, thyroid, esophagus and ovary: and the remainder (all other organs together).

Excess relative risk: (ERR) = $\beta s\, D\, .\exp [_{\gamma} (e-30) + {}^{\eta} \log (a/70)]$

Where βs is referred to β male or β female which means sex specific estimation of ERR per Sv.D = mean organ dose (Sv),e = age at exposure (years) and a = attained age (years)
Excess absolute risk:(EAR) = βs D .exp [$_{\gamma}$ (e-30)+ $^{\eta}$ log (a/70)]
The coefficients β male, β female, $_{\gamma}$, $^{\eta}$, are given in tables 4.2, 4.3 of ICRP Publication 103 for (ICRP, 2007) for ERR and EAR in terms of cancer incidence. [10]
Estimation of the lifetime Risk

The estimation of the Lifetime Risk of radiation induced cancer incidence in various organs was calculated using Table 4.4 and 4.5 The life time risk values of cancer incidence for several solid tumors were tabulated as a function of age and sex for a composite Euro-American population (% per Gy) at the time of exposure.

IV. Result And Discussion

Absorbed doses in various Organs at Risk (OARs) are estimated for ten prostate patients with prostate cancer and the mean absorbed dose in each organ is obtained. This information is determined from the DVHs.The mean absorbed dose measurements for 3D-CRT and IMRT.

Table 1: The mean absorbed dose measurements for 10 prostate cancer patientsin3D-CRT and IMRT.

ID/ modality	Rectum		bladder		Colon	
	3D-CRT	IMRT	3D-CRT	IMRT	3D-CRT	IMRT
1	32.61	30.12	38.02	33.85	0.04	0.16
2	41.47	29.85	37.62	35	0.12	0.52
3	36.45	35.42	43.52	42.7	0.2	0.87
4	67.69	58.04	47.6	43.5	0.3	0.91
5	58.28	47.01	46.2	44.5	0.22	0.43
6	48.87	60.23	33.45	23.77	0.17	0.36
7	51.48	48.76	39.01	34.02	0.12	0.51
8	23.7	32.42	37.87	29.73	0.03	0.49
9	46	43.52	36.54	38.2	0.045	0.83
10	43.5	36.54	38.53	36.4	0.05	0.68

It must be mentioned that, in-field region is assigned as all tissues within the trans-axial planes of PTV. The mean dose in Gy and the SD of therapeutic dose at the rectum, bladder and colon for 3D-CRT were (45±12.67), (39.83±4.48) and (0.13±0.09), respectively. For IMRT, the doses were (42.19±11.13), (36.17±6.47) and (0.57±0.24), respectively. The mean dose for infield OARs (rectum and bladder) in IMRT is lower than 3D-CRT However, for out of field OAR (colon) the dose received is higher in IMRT than in 3D-CRT.
The graphical representation of the data in table 1 is illustrated in Fig 1

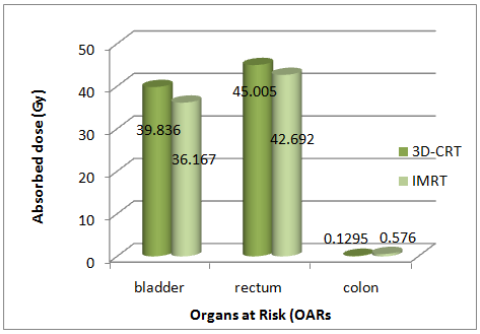


Figure 1: Average absorbed doses in various OARs for 10 prostate patients treated using 3D-CRT and IMRT technique.

Comparing results with[Kry SK et al 2005, Howell RM et al 2006 and Mutic S et al 1998] [11, 12, 13] It is recommended that bladder should be full to reduce the bladder dose. IMRT resulted in a significantly reduction for rectal dose V15%, V25%, V35% and V50% where the P values were P = 0.0001, P<0.0001, P= 0.0004 and P=0.0037, which is highly significant and this radiobiological peculiarity has the effect of increasing the risk of a second malignancy [Kry SK et al 2005 and Followill D et al 1997]. [11, 14]

The Lifetime Risk in various OARs due to two different modalities 3D-CRT and IMRT

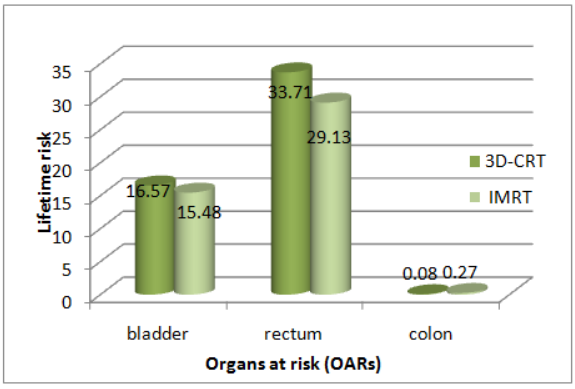


Figure 2: The average of Lifetime Risk for patients due to 3D-CRT and IMRT

Figure 2 shows that the average LifetimeRisk for bladder and rectum infield OARs for male patients in 3D-CRT is higher than that of male patients in IMRT of the same age of the two groups. For colon outfield OAR there is low difference can be observed between the Lifetime Risk values but we obtain that low dose from IMRT is higher than that of 3D-CRT.

Bednarz B et al 2010,[15] reported that LAR decreases as a function of age at exposure, which is a general feature of the risk model. This is intuitive since older patients are less likely to live long enough to develop a second primary cancer. Also, for a given treatment plan, the organs with the highest risks are typically closer to the primary beam suggesting that higher radiation doses contribute to higher second cancer risks. However, this is not always the case. For example, even though the thyroid receives higher dose than the brain, the second cancer risk in the thyroid is lower than the brain for all treatments.

Kim DW 2014, [16] studied the secondary cancer risk in prostate cancer patients and estimated the incidences of extra solid tumors after radiotherapy (Brenner DJ et al 2000).[17]They reported, among 17,327 persons at risk, 139 extra solid tumors were estimated to be induced by radiation treatment. This indicates that the sum of LARs due to the prostate radiotherapy is approximately 0.27% which is less than the risk with HCC treatment. This may be due to the fact that the exposed age is high and the number of organs at risk is few for prostate cancer treatment compared to HCC treatment. This comparison indicates that the LAR value is critically dependent on the site of cancer and the exposed age.

V. The Excess Absolute Risk (EAR) For Oars Due To 3D-CRT And IMRT

Excess absolute cancer risk calculated for ten cancer prostate patients, for the OARs due to 3D-CRT and IMRT as a function of age at exposure and sex and by putting attained age 70 years old and by using mean organ dose and calculating it from DVHs, are illustrated in fig 3

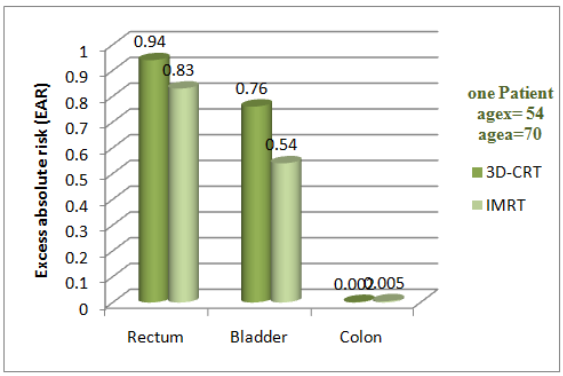


Figure3: The Excess Absolute Risk (EAR) for OARs due to 3D-CRT and IMRT for prostate cancer for one patient.

Table 2 Show means ±SD of EAR for prostate patients using 3D-CRT and IMRT. The EAR for bladder and rectum (infield OARs) using 3D-CRT is higher than that of IMRT. For colon outfield OAR there is low difference between the EAR values using the two modalities but we obtain that low dose from IMRT is higher than that of 3D-CRT which increase the probability of radiation induced second primary cancer

Table2: The mean ± SD of EAR for prostate patients using 3D-CRT and IMRT

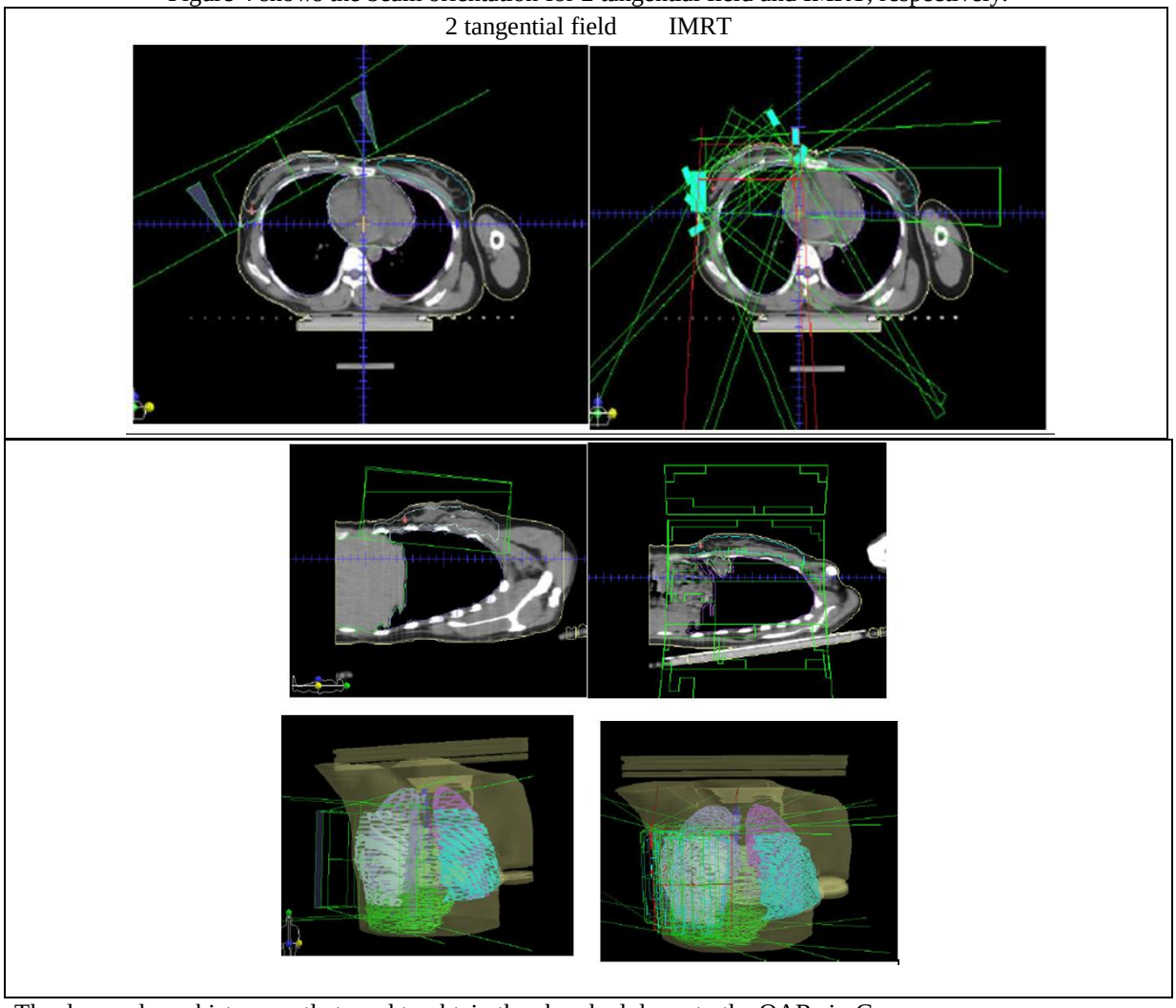
Modality / OAR	3D-CRT Mean ± SD	IMRT Mean ± SD
rectum	1.70±1.71	1.4±01.26
bladder	1.15±0.628	1.05±0.614
Colon	0.006±0.0062	0.018±0.019

The risk of developing cancer of the rectum after radiation therapy for prostate cancer is similar to the risk of having a first-degree relative with colorectal cancer. There is evidence that radiation shifts the patients from normal to moderate risk for rectal cancer. Baxter and colleagues reported a significant increase in the development of rectal cancer, indicating that the effect was specific to directly irradiated tissue. The observed hazard ratio for radiation therapy and subsequent rectal cancer was 1.7 [(18)] Results from the SEER database estimated the relative risk of rectal cancer developing after EBRT, brachytherapy, and EBRT brachytherapy compared with radical prostatectomy to be 1.26, 1.08, and 1.21, respectively. [(19)]

There is evidence that patients diagnosed with prostate cancer share an increased relative risk for primary bladder cancer occurrence irrespective of the treatment modality used. [(20, 21)]In the vast majority, the secondary bladder carcinomas are high grade and muscle invasive at diagnosis. Moreover, bladder cancer-specific survival is worse in the population of patients who present with secondary bladder cancer following radiation for prostate cancer versus patients not treated with radiation.[(20)]

Right breast cases

Figure 4 shows the beam orientation for 2 tangential field and IMRT, respectively.



The dose volume histogram that used to obtain the absorbed doses to the OARs in Gy

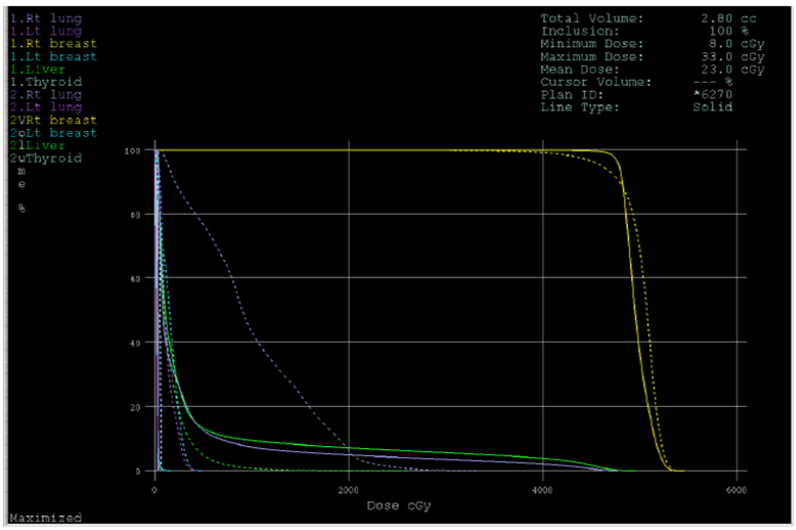


Figure 5:Dose-volume histogram (DVH) for 2 tange (solid line) and IMRT (dashed) plans. Color for right lung (light blue), left lung (purple), heart (light green), right breast (yellow), left breast (cyan) liver (green) and thyroid (light cyan).

Comparison for treatment planning information

Table 3: Treatment planning information for five right breast cancer patients

ID	Modality	No . of fields	MU/Gy
1	3D-CRT IMRT	2 7	344 497
2	3D-CRT IMRT	2 7	389 542
3	3D-CRT IMRT	2 7	269, 633
4	3D-CRT IMRT	2 7	445 715
5	3D-CRT IMRT	2 7	327 567

Table 3 compares the treatment plans for different modalities where seven fields were used for each IMRT plan, the total monitor units (MU) ranged from 497 to 715 MU/Gy. For 3D-CRT two Tangential fields were used, the total MU ranged from 269 to 445 MU/Gy. From the results, we obtain that the total MUs in IMRT is higher than that of 2 tange. Then More MUs were needed for larger PTV size for IMRT but MU of 2 tange was not depended significantly for PTV size. In addition, the value of MU per Gy depends on the modality. 2 tange uses fewer MUs than IMRT. Therefore, 2 tange facilitates shorter treatment times and fewer MUs than of IMRT.

These results are in agreement with that of Kim DW et al 2014, [(16)] who reported that more MUs were needs for larger PTV size for IMRT and TOMO but MU of VMAT was not depended significantly for PTV size. In addition, the value of MU per Gy depends on the modality. VMAT had a relatively small amount of total treatment MUs than that of IMRT, and no significant dependency with PTV size. TOMO had a comparably large amount of treatment MU than that of IMRT. As reported in previous studies, VMAT uses less MUs than IMRT and TOMO. Therefore, VMAT facilitates shorter treatment times and fewer MUs that are related to patient immobilization and machine maintenance.

The Excess Relative Risk (ERR) for OARs due to 2- tangential and IMRT

Excess relative cancer risk calculated for right breast cancer patients, for the OARs due to 2- tangential and IMRT as a function of age at exposure and sex using equation 4.2, putting attained age 70 years old and using mean organ dose. Figures represent the ERR with age of exposure for OARs between 2- tangent and IMRT.

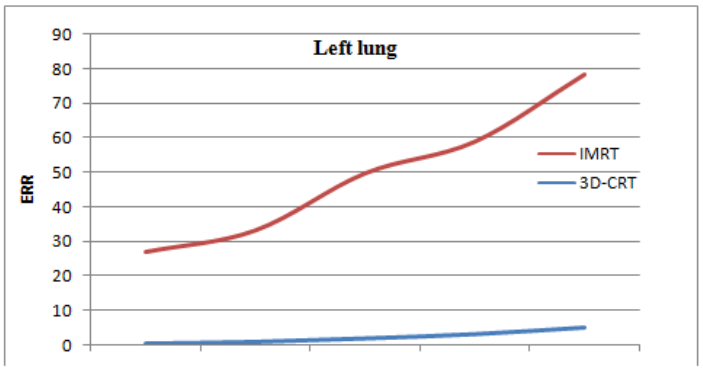


Figure 6: The Excess relative risk (ERR) with age of exposure for left lung between 3D-CRT and IMRT.

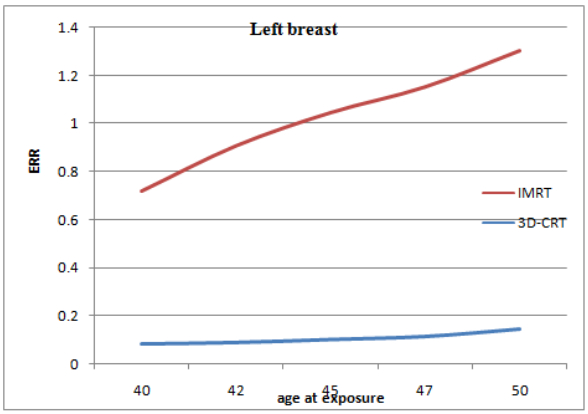


Figure 7: The Excess relative risk (ERR) with age of exposure for left breast between 3D-CRT and IMRT.

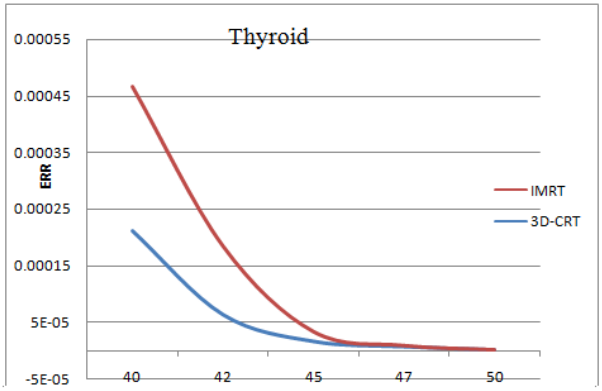


Figure 8: The Excess relative risk (ERR) with age of exposure for thyroid between 3D-CRT and IMRT.

According to Shuryak I et al, [17] the ERR/Gy estimates from Japanese atomic bomb survivors at age 70, as function of age at exposure, were fitted quite well for all cancer types. In the context of our model, the shape of the dependence of radiation-induced ERR on age at exposure provides insight into whether this ERR is dominated by initiation or promotion. Initiation driven ERR should decrease markedly with age at exposure. In contrast, promotion-driven ERR should be relatively constant as function of age. The atomic bomb survivor data (Preston DL et al. 2007) [22] suggest that a substantial decrease in ERR/Gy with age at exposure occurs only for stomach and thyroid cancers, among those analyzed here. For the seven other cancer types, ERR/Gy appears to be independent of age at exposure, or even to increase at older ages.

Recent analyses of atomic bomb survivor data (Little MP 2009; Walsh L(2009) [23, 24] suggest that an apparent increase in ERR/Gy for the oldest ages at exposure may occur for several other cancer types in addition to lung cancer. This phenomenon can be due to multiple factors, e.g. activation of microscopic dormant tumors by radiation. The explanation given by the current model for lung cancer is also a plausible hypothesis for explaining these new data for other cancers.

Left breast cases: Absorbed doses in various OARs due to 3D-CRT and IMRT

Absorbed doses in various Organs at Risk (OARs) are estimated for ten left breast cancer patients.

Table 4: Represents the mean absorbed dose of therapeutic dose measurements for 3D-CRT and IMRT

ID	Modality/ Organ	Organ absorbed dose per Gy				
		Left lung	Right lung	Right breast	Thyroid	Liver
1	3D-CRT	10.16	0.18	0.07	0.34	0.35
	IMRT	12.59	3.45	1.1	0.41	3.21
2	3D-CRT	9.84	0.15	0.7	0.37	0.42
	IMRT	10.2	2.47	1.09	0.55	2.94
3	3D-CRT	5.88	0.18	0.12	0.23	0.17
	IMRT	10.81	2.26	1.43	0.52	2.1
4	3D-CRT	6.95	0.14	0.1	0.36	0.31
	IMRT	11.49	1.93	1.36	0.41	2.8
5	3D-CRT	5.03	0.15	0.11	0.19	0.38
	IMRT	9.71	1.8	1.54	0.56	3.05
6	3D-CRT	3.84	0.17	0.14	0.3	0.27
	IMRT	8.67	2.46	2.36	0.62	3.01
7	3D-CRT	9.62	0.21	0.08	0.29	0.4
	IMRT	12.81	2.31	1.17	0.9	3.08
8	3D-CRT	3.54	0.16	0.18	0.26	0.19
	IMRT	8.32	2.63	3.09	0.49	2.4
9	3D-CRT	4.3	0.2	0.13	0.32	0.41
	IMRT	8.49	1.53	1.77	0.78	2.93
10	3D-CRT	8.61	0.19	0.09	0.27	0.63
	IMRT	11.87	2.46	1.28	0.41	2.64

The mean doses in Gy ± SD of therapeutic dose at the left lung, right lung, right breast, thyroid and liver for 3D-CRT were (6.78±2.61), (0.173±0.02), (0.11±0.03), (0.293±0.06) and (0.35±0.13). For IMRT were (10.5±1.68), (2.33±0.52), (1.62±0.64), (0.57±0.18) and (2.82±0.34), respectively. The mean doses for OARs in left breast cases in IMRT are higher than in 3D-CRT.

The Lifetime Risk in various OARs due to two different modalities 3D-CRT and IMRT for ages from 40 and 57 years

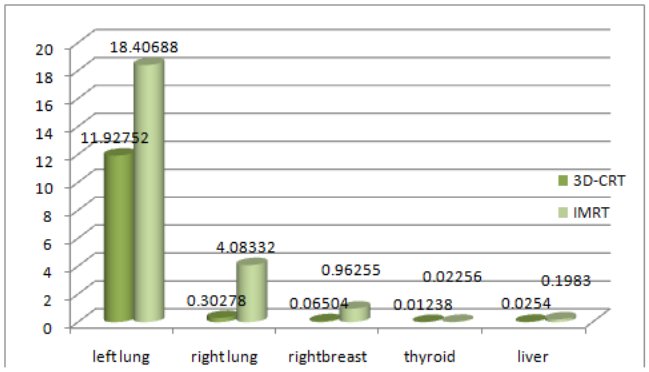


Figure 9: The average Lifetime Risk for patients from 40-57 years old female patients due to 3D-CRT and IMRT.

Figure 9 illustrates that the average Lifetime Risk for left lung, right lung, right breast, thyroid and liver OARs for left breast female patients in 3D-CRT and IMRT. The figure shows that left lung, right lung, right breast in IMRT is higher than that of 3D-CRT.

VI. Conclusions

The results showed increase in dose for out of field OAR with IMRT plan comparing to 3D-CRT where larger volume is irradiated to lower doses where the total MUs in IMRT is higher than that of 3D-CRT which increases the probability of induction of second primary cancer in out of field OAR in IMRT than in 3D-CRT while for OARs in infield with IMRT receive lower dose allowing significant reduction in the doses in infield OAR compared to 3D-conformal which decrease probability of induce of second primary cancer in out of field OAR in IMRT than in 3D-CRT

For prostate cases bladder and rectum infield OAR receives less dose in IMRT than 3D-CRT while colon out of field OAR receives higher dose in IMRT than 3D-CRT.

For breast cases out of field OAR thyroid and liver receives higher dose in IMRT than 3D-CRT (in low dose). By comparing contralateral lung and contralateral breast they take higher dose in IMRT than 3D-CRT because breast takes two tangential beams in 3D-CRT where contralateral lung and contralateral breast are away from the exit of the beams, however in IMRT contralateral lung and contralateral breast receive dose from the exit of the beams.

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